

Review Article



Peptide Drug Conjugates (PDCS): The Next Generation of Targeted Therapy

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ABSTRACT

Peptide-Drug Conjugates (PDCs) represent the next technological step forward in targeted cancer therapy, building on the framework established by Antibody-Drug Conjugates. The aim of the research in this field is to develop highly selective and potent agents capable of delivering an ultra-toxic payload directly into malignant cells. This should maximize the therapeutic efficiency while at the same time minimizing systemic damage. This rationale for the research is underpinned by the inherent advantages of peptides, as their small molecular size, 2-20 kDa, allows superior tumour penetration and low immunogenicity, enabling cost-efficient and highly homogeneous synthesis. PDCs are modular systems made of a tumour-homing peptide, chemical linker, and cytotoxic payload. Most research is focused on the attempts of overcoming core limitations, such as a short half-life because of rapid renal clearance and metabolic instability of a peptide backbone. The results of clinical translation reflect these problems faced by this class of drug conjugates. Currently, only the radionuclide PDC Lutathera has retained FDA approval, whereas Pepaxto, melphalan flufenamide, has seen its approval withdrawn from the US market. Despite those regulatory and technical barriers, the conclusion remains optimistic. The field is rapidly moving with the implementation of advanced peptide modification technologies, like cyclization and PEGylation, and the strategic integration of Computational Software and Artificial Intelligence methods for rational de novo design and in silico screening, which accelerate the development of a new generation of stable and highly effective targeted treatments for cancer.

Keywords: Antibody-drug conjugate; Cancer; Drug delivery system; Peptide-drug conjugate; Targeted therapy.

INTRODUCTION

The history of cancer treatment is a compelling narrative of continuous progress, moving dramatically from broadly toxic approaches to highly sophisticated, selective therapeutic strategies. For a considerable period, the standard-bearer in the fight against malignancy was traditional chemotherapy. This method, while indispensable, operated on a principle of non-selective toxicity, essentially targeting all cells that divide rapidly. While this effectively attacked aggressive tumour cells, it simultaneously ravaged healthy, rapidly proliferating tissues—such as the bone marrow, hair follicles, and the gut lining—leading to severe, life-altering side effects¹. This inevitable collateral damage severely compromised patients' quality of life and often forced dose reductions, which inadvertently limited the full anti-tumour potential of the drugs. This inherent lack of distinction between healthy and cancerous cells underscored the urgent and critical need to develop treatment modalities that could deliver their potent therapeutic payload precisely and exclusively to the site of the disease. This imperative for localized treatment sparked a transformative wave of research focused on creating sophisticated drug delivery systems². The initial and most prominent manifestation of this new paradigm was the development of Antibody-Drug Conjugates (ADCs). The conceptual foundation of an ADC is rooted in molecular biology, where a highly specific monoclonal antibody—a protein engineered to recognize and bind to a unique antigen overexpressed on the cancer cell surface—is chemically linked to an extremely potent, cytotoxic drug. In this system, the antibody acts as a

precision guidance system, navigating the body's complex biological terrain to lock onto the malignant cells³. Upon binding, the entire complex is usually internalized by the cancer cell through a process called endocytosis. Once inside, the linker connecting the antibody and the drug is cleaved, releasing the active drug to destroy the cell locally. This strategic compartmentalization of the drug represented a monumental leap forward, demonstrating that selective delivery could drastically reduce systemic exposure and, consequently, debilitating side effects, thereby establishing the foundational framework for targeted cancer therapy⁴.

Building upon the established success and the core framework of ADCs, oncology researchers have propelled the field toward next-generation targeted therapeutics, epitomized by the emergence of Peptide-Drug Conjugates (PDCs). A PDC is fundamentally designed as an active prodrug; it is stable, inactive, or minimally active while circulating freely in the bloodstream, only becoming fully active once it reaches its intended destination. The profound clinical rationale for adopting PDCs is intimately linked to the unique biological and physiochemical attributes of the constituent peptides⁵. Unlike the much larger, high-molecular-weight antibodies (typically around 150 kDa), peptides are significantly smaller, generally ranging from 2 to 20 kilodaltons (kDa). This smaller size is a substantial asset, granting them a superior ability to penetrate solid tumour masses effectively. Solid tumours are notorious for their dense structure, high interstitial fluid pressure, and often chaotic, poorly perfused vasculature, which acts as a physical barrier to large molecules. PDCs,



due to their diminutive stature, can navigate this constrained environment much more efficiently, allowing for a deeper and more homogeneous distribution of the drug throughout the tumour volume⁶.

Furthermore, peptides are selected or engineered for their rapid, high-affinity binding to specific overexpressed tumour-associated receptors, such as the Somatostatin Receptor (SSTR) or the Luteinizing Hormone-Releasing Hormone (LHRH) receptor. This rapid engagement mechanism contributes to quick accumulation at the tumour site. This small size advantage is critically important for targeting non-vascularized, dense tumour microenvironments (TMEs), ensuring that even remote areas of the tumour receive a therapeutic concentration of the drug, thus reducing the risk of developing pockets of drug resistance⁷. The ultimate efficacy of a PDC is contingent upon a meticulously orchestrated sequence of events: first, its ability to selectively accumulate at the tumour site by exploiting receptor overexpression; second, its efficient internalization into the cancerous cell through the process of receptor-mediated endocytosis; and finally, the controlled release of the active drug via a mechanism

designed to be activated by the specific pathological conditions within the tumour cell (such as low pH or high concentrations of specific lytic enzymes). This controlled liberation maximizes the drug concentration precisely where it is most needed—inside the cancer cell—which is the essence of modern, precision oncology. This progression from systemic toxicity to molecular-level precision confirms the trajectory of cancer treatment toward strategies that are both powerful against the disease and profoundly more compassionate to the patient⁸.

COMPARISON BETWEEN ANTIBODY-DRUG CONJUGATES (ADCs) AND PEPTIDE-DRUG CONJUGATES (PDCs):

The common three-component structure shared by ADCs and PDCs belies basic differences in their physicochemical properties, which determine fundamentally different pharmacokinetics and clinical profiles. Much smaller in dimensions, PDCs must be designed to overcome the penetration issues of the large (~150 kDa) antibody backbone common to ADCs. Moreover, control over the Drug-to-Ligand Ratio, or DLR, is a key advantage for the PDCs, which affects homogeneity and efficacy⁹. The comparison between ADC and PDC is given in the Table 1.

Table 1: Comparative Features of Antibody-Drug Conjugates (ADCs) and Peptide-Drug Conjugates (PDCs)

Feature	Antibody-Drug Conjugates (ADCs)	Peptide-Drug Conjugates (PDCs)	Citation
Size (Molecular Weight)	High (~150 kDa)	Low (2–20 kDa)	11
Tumour/Tissue Penetration	Limited; large size hinders diffusion into dense tumours.	High; small size allows rapid and deep tissue penetration.	12
Industrial Synthesis/Cost	Complex and expensive synthesis; results in heterogeneity (variable DAR).	More accessible industrial synthesis and lower cost; yields high homogeneity.	11,12
Immunogenicity	Moderate to High; risk of anti-drug antibodies (ADAs).	Low; peptides generally have low intrinsic immunogenicity.	13
Systemic Clearance	Slower clearance (long half-life, days to weeks).	Rapid clearance (short half-life, minutes to hours); prone to renal filtration.	14
Major Challenge	Off-target liver/ haematological toxicity, heterogeneity.	Poor metabolic stability, rapid renal clearance, and potential nephrotoxicity.	14, 15

IMPROVING ENZYMATIC AND CHEMICAL STABILITIES OF PEPTIDES BY CHEMICAL MODIFICATION:

Poor enzymatic stability, or inherent susceptibility of the native peptides to rapid enzymatic degradation by proteases, and poor pharmacokinetics, or rapid elimination via renal filtration, are major hurdles. The methods to improve the enzymatic and chemical stability of PDCs is depicted in fig 1.

1. Enhanced Cell-Penetration

To function inside a cell, peptides must overcome the barrier of the cell membrane. This is achieved by:

- **Amphiphilicity:** Designing the peptide with distinct polar and hydrophobic segments allows it to interact favourably with the lipid bilayer, facilitating passage.
- **Electrostatic Attraction:** Incorporating positive charges into the sequence encourages binding to the negatively charged cell surface components, promoting uptake.

- **Chimeric Design:** Creating chimeric sequences allows researchers to fuse a cell-penetrating motif with a therapeutic domain, yielding a functional peptide that can reach its intracellular target.

2. Stimuli-Responsive Design

These peptides are built for targeted and controlled release, often in specific disease microenvironments:

- **Enzymatic Triggering:** Peptides can incorporate an enzyme-labile bond (like a disulfide bond) that is stable in circulation but is specifically cleaved by enzymes overexpressed in a target area (e.g., tumours), causing the peptide to activate or release its payload¹⁶.
- **pH Sensitivity:** A change in the local pH (such as the slightly acidic environment of tumours or endosomes) can trigger a conformational change, causing the peptide to switch from a monomer state to an aggregate or hydrogel structure for localized action or sustained release.



3. Stability Improvement

Natural peptides are often quickly degraded *in vivo*, so stabilization is essential for drug delivery:

- **Physical Stability:** Enhancing the overall structural integrity can lead to better formulation, such as enclosing the peptide within a liposome to protect it from the environment and prolong its half-life.

- **Chemical/Enzymatic Stability:** This is often achieved through structural constraints:

- **Stapling and Stitching:** These techniques introduce covalent cross-links (internal bridges) within the peptide chain. This process locks the peptide into a rigid, favourable structure, leading to improved helicity (e.g., stabilizing an α -helix). This constrained structure is significantly more resistant to enzymatic degradation and hydrolysis, boosting both chemical and enzymatic stability¹⁷.

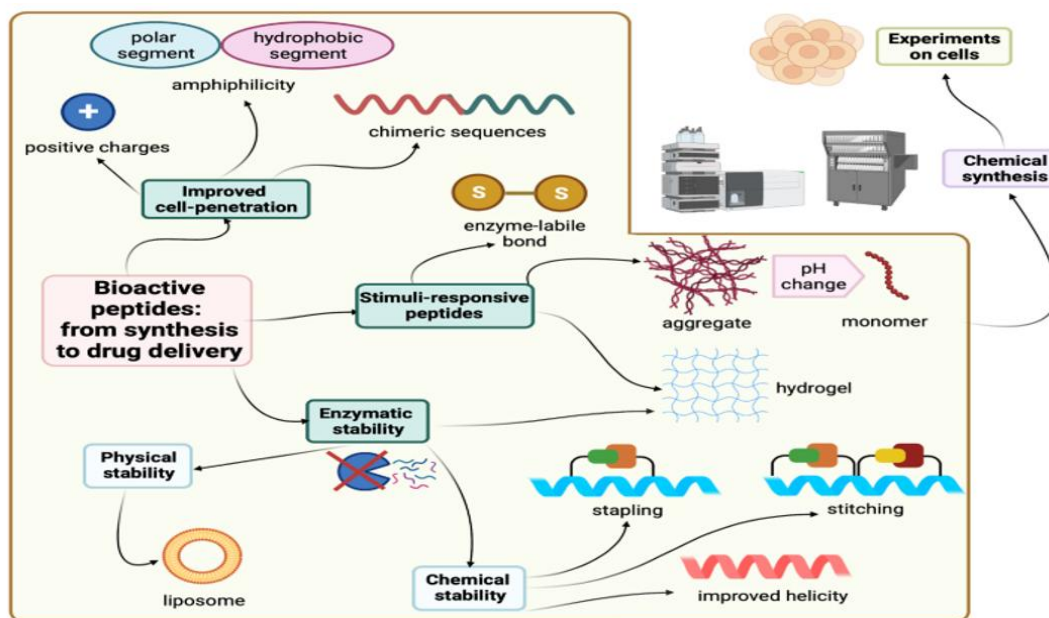


Figure 1: Strategies for enhanced peptide stability

KEY COMPONENTS OF PDC:

A. Peptides

It is in the peptide constituent that the major homing device resides, critical to specificity and internalization. Categorization: PDCs employ cell-targeting peptides for receptor binding, for example, SSTR, LHRH, Folate Receptor, cell-penetrating peptides for improved membrane translocation, and newer Bicyclic Peptides for high stability and affinity¹⁸. Control of Drug Release, Increase in Drug Loading, and Efficacy: The peptide platform enables the fabrication of peptide dendrimers or self-assembled peptide nanocarriers to enable multivalent display-increasing avidity-and load many drug molecules per peptide unit, hence increasing the Drug-to-Ligand Ratio (DLR)¹⁹. Improving Drug Bioavailability: Poor systemic stability and poor bioavailability are overcome with the strategies discussed in Section 6, namely PEGylation, lipidation, albin-binding.um

B. Linker:

The linker is the critical bridge that provides stability in circulation and controlled release intracellularly. The nature of the linker controls the mechanism of drug activation. The classification of different linkers is given in Table 2.

TYPES OF LINKERS:

1. Cleavable Linkers (Activated Release):

- Designed for stability in the blood but to break apart upon arrival at the tumour.
- Release is triggered by tumour conditions, including low pH, high enzymes (such as Cathepsin B), and reducing agents.
- It ensures potent drug release inside the cancer cell, mainly after internalization²¹.
- Goal is maximized local efficacy and minimized systemic toxicity.

2. Non-Cleavable Linkers (Metabolic Release):

- Chemically stable and robust, they do not break in circulation or due to environmental triggers.
- The drug release occurs only after complete degradation of the conjugate inside the lysosomes of the cell²².
- The drug released is attached to a single amino acid remnant.
- The main advantage is higher stability in the blood, causing less early release of the drug.

3. Self-Immolative Linkers (Cascade Release):

- Specialized system in which the breaking of one bond leads to a rapid subsequent chemical cascade.
- This cascade causes the residual linker structure to self-destruct spontaneously.
- Ensures that the active drug molecule is released cleanly and quickly after the first trigger event.
- Designed for high efficiency and complete release of the intact, active drug payload.

4. Bifunctional linkers (synthesis tool):

- These are chemical reagents with two different reactive functional groups.
- Their major role is to precisely link the peptide and the drug payload during synthesis²³.
- Allows the chemist to control exactly the site of drug attachment on the peptide.

- Crucial for ensuring controlled synthesis and a stable conjugation structure.

C. Payloads

The payload has to be ultra-toxic to compensate for the limited mass that reaches the intracellular space to ensure the eradication of cancer cells.

Cytotoxic Drugs: Commonly, these are highly potent tubulin inhibitors such as Auristatins, e.g., MMAE, or DNA damaging agents like derivatives of Melphalan, e.g., Melflufen. Warhead selection is critical to the elimination of target cells²⁸.

Radionuclides: The peptide is coupled to a radioactive isotope, such as ¹⁷⁷Lu or ⁶⁸G for Radioligand Therapy (RLT), or for diagnostic imaging. Examples include the FDA-approved ¹⁷⁷Lu-DOTATATE (Lutathera).

Table 2: Classification of Different Linkers Based on Release Mechanism

Linker Classification	Cleavage Mechanism (Trigger)	Example Moiety/Sequence	Therapeutic Implication	Citation
Enzyme-Cleavable	Cleavage by overexpressed lysosomal enzymes (e.g., Cathepsin B).	Valine-Citrulline (Val-Cit) sequence.	Drug released after receptor-mediated endocytosis and lysosomal degradation.	24
Reduction-Sensitive	Cleaved by high concentrations of thiols.	Disulfide Bonds.	Cleavage occurs inside the cell due to the 100-1000 fold higher concentration of Glutathione (GSH) in the cytosol.	25
pH-Sensitive	Hydrolysed under acidic conditions.	Hydrazone or cis-Aconityl bonds.	Cleavage occurs in the acidic TME or endosomes/lysosomes pH 4.5-5.5.	25, 26
Non-Cleavable	Requires complete proteolytic degradation of the peptide and linker complex.	Highly stable Thioether bonds.	The drug is released still attached to a single amino acid. Used in many peptide-radionuclide conjugates.	27

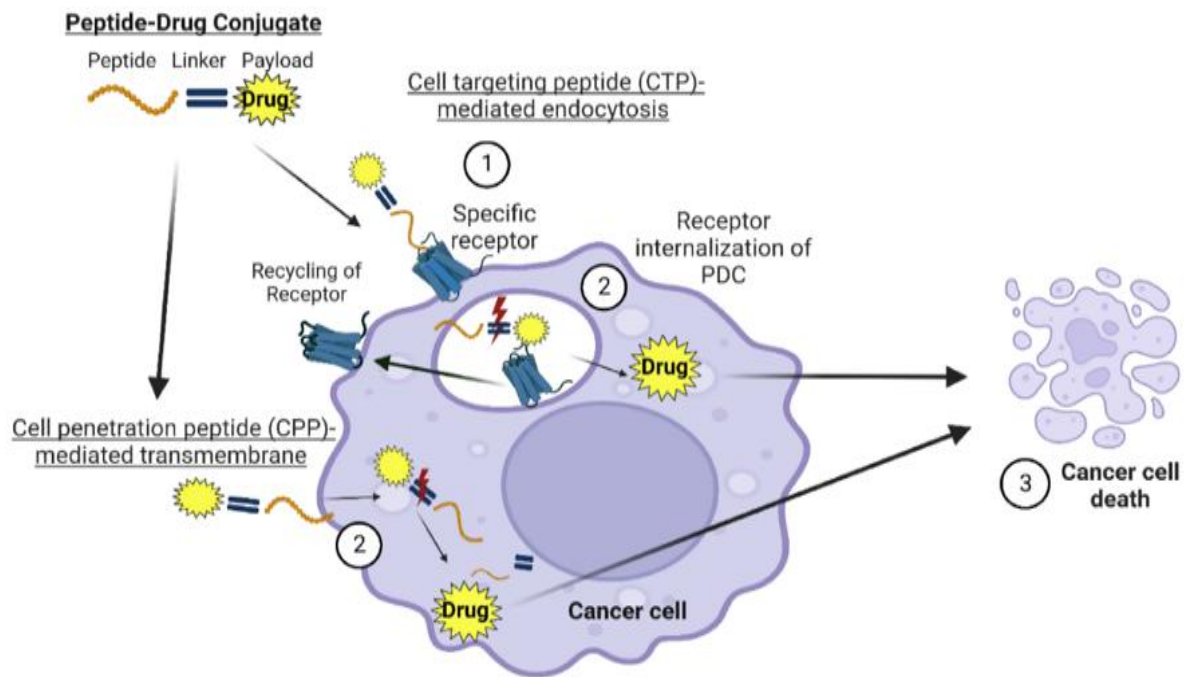


Figure 2: Targeting and Internalization of Peptide-Drug Conjugates via CTP and CPP Strategies

CANCER THERAPY AND TARGETED DRUG DELIVERY:

Targeted drug delivery, as accomplished by PDCs, takes advantage of molecular differences between malignant and normal cells. Specificity is ensured by active targeting via the peptide moiety and, inherently, passive targeting via the EPR effect. The small size of the PDCs provides for much better permeation into solid tumour masses when compared to large ADCs. The mechanism of targeted therapy is depicted in fig 2.

- **Specific homing:** the peptide seeks out and binds to receptors uniquely abundant on cancer cells.
- **Tumour penetration:** The small size of PDCs allows for easy and deep infiltration into the dense tumour tissue.
- **Internal Release:** The PDC is pulled into the cell, where the linker is cleaved by the harsh internal environment to release the drug.
- **Localized Killing:** The released drug acts locally in order to kill the cancer cell, minimizing toxicity in healthy organs because of rapid clearance from the body.

SYNTHESIS OF PDC:

The manufacturing of Peptide-Drug Conjugates (PDCs) relies on a precise, two-stage modular approach that leverages established synthesis techniques to ensure a structurally homogeneous final product.

1. Peptide Synthesis and Functionalization

The Peptide component of the PDC is manufactured using Solid-Phase Peptide Synthesis (SPPS).

- SPPS is a matured technology that allows for the precise, step-by-step assembly of the amino acid sequence, building the peptide chain one residue at a time while anchored to a solid resin.
- **Functionalization:** During this synthesis, a specific, highly reactive functional group (such as a thiol or an azide) is strategically incorporated at a desired location on the peptide. This group will serve as the unique chemical handle for the subsequent conjugation step³¹.

2. Final Conjugation

In the second stage, the fully synthesized and functionalized peptide is joined with a pre-fabricated linker-payload intermediate (the drug attached to the linker). This step requires highly selective and efficient reactions.

- **Bioconjugation Chemistry:** The goal is to unite the two components with high specificity and yield, ensuring a structurally homogeneous final product (meaning all PDC molecules are identical).
- **Preferred Reactions:** Reactions used for this final conjugation are chosen for their high efficiency (high yield) and mild conditions (which prevent damage to the sensitive peptide or drug molecule). Common examples include:

- **Click Chemistry (Alkyne-Azide Cycloaddition):** A powerful and reliable reaction where an alkyne group on one component rapidly reacts with an azide group on the other component to form a stable triazole ring.

- **Thiol-Maleimide Reaction:** A widely used reaction involving the highly selective addition of a thiol group (on the peptide) across the double bond of a maleimide group (on the linker-payload), forming a stable thioether bond³².

This modular strategy ensures both the accurate synthesis of the complex peptide and the efficient, precise attachment of the drug payload.

Pharmacokinetics and dynamics of PDC:

The PK of PDCs is dominated by their low molecular weight, leading to rapid renal filtration and a short plasma half-life, often in the range of minutes to hours. Stabilizing modifications are necessary to prolong their circulation time³³. The main determining factor of PD is Target-Mediated Drug Disposition, in which the concentration of the drug decreases as it binds to a target receptor³⁴. The produced therapeutic effect is the highly localized, strong cytotoxic effect resulting from the high concentration of the drug released inside the tumour cell³⁵.

How a PDC targets the desired tissue:

The mechanism of a Peptide-Drug Conjugate involves a structured cascade of events designed to maximize therapeutic effect within the tumour while minimizing systemic toxicity. First, Systemic Stability is important; this ensures that the conjugate remains chemically intact and protected while circulating in the bloodstream. Delivery then relies on a two-pronged targeting approach³⁶. Passive Accumulation occurs first, where the relatively small size of the PDC allows utilization of the Enhanced Permeability and Retention (EPR) effect to accumulate within the leaky, disorganized vasculature of the tumour. Following this, Active Homing takes place as the peptide component of the molecule specifically recognizes and binds with high affinity to overexpressed tumour-associated receptors on the cancer cell surface³⁷. This binding triggers Internalization via receptor-mediated endocytosis, which engulfs the entire PDC complex into acidic endosomal vesicles. The final, critical step is Intracellular Drug Release; inside the lysosome, the acidic pH and high concentrations of hydrolytic enzymes-like Cathepsin B-cleave the linker to liberate the free, active cytotoxic payload. This released drug then executes its therapeutic function through action on its specific molecular target, such as DNA or microtubules, leading to localized cell death³⁸. The tumour targeting strategies are given in the Table 3.

Stability of PDC:

Optimal stability is a critical balance between maintaining integrity in the blood and allowing efficient cleavage in the target cell. **Chemical Stability:** The stability of the linker-payload bond against non-specific hydrolysis in the plasma. **Enzymatic Stability:** The resistance of the peptide carrier to degradation by systemic proteases and peptidases³⁹. This is



often enhanced by D-amino acid substitutions and achieved through size-increasing modifications like cyclization. Pharmacokinetic Stability: The ability of the PEGylation or the use of alternative long-circulating molecule to resist rapid renal elimination, primarily polymers like PAS.

Table 3: Tumour-Targeting Strategies by the PDC Peptide Component

Strategy	Mechanism of Targeting	Representative Targets/Examples	Peptide	Receptor/Target Type	Citation
Cell-Targeting Peptides (CTPs)	Selective binding to receptors overexpressed on cancer cell membranes, initiating endocytosis.	Octreotide (Somatostatin analogue), PSMA ligands.		Somatostatin Receptors (SSTRs), PSMA.	28, 29
Cell-Penetrating Peptides (CPPs)	Translocation across the cell membrane in a receptor-independent manner.	Tat, Poly-arginine.		Cell Membrane (Translocation).	29
Microenvironment Targeting	Targets non-cancerous components of the Tumour Microenvironment (TME).	Peptides targeting tumour-associated stroma or specific proteases (e.g., MT1-MMP).		Tumour Stroma, MMPs.	30

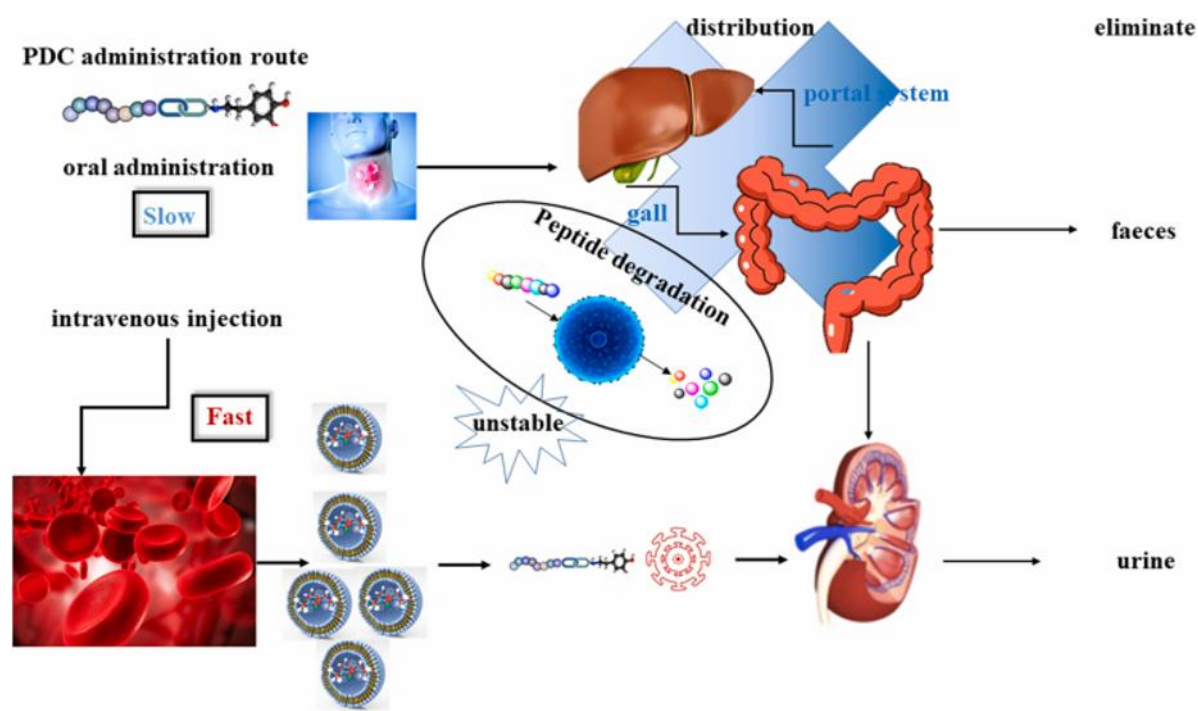


Figure 3: The relationship between the PDC delivery route and drug stability *in vivo*.

Table 4: Clinical Examples and Status of Key Peptide Drug Conjugates (PDCs)

PDC Name	Targeting Peptide/ Ligand	Payload/ Warhead	Indication/Target	Clinical Status & Key Notes	Citation
Lutathera (¹⁷⁷ Lu-DOTATATE)	Octreotide (SSTR analogue)	Lutetium-177 (Radionuclide)	Neuroendocrine Tumours (NETs)	FDA and EMA Approved (2018). Benchmark success of PDCs/RLT.	41
Pepaxto (Melphalan Flufenamide)	Oligopeptide carrier	Melphalan (Alkylating Agent)	Multiple Myeloma	Voluntarily Withdrawn from US Market (2022) due to unfavourable survival data; retains EMA/MHRA approval.	42
BT1718	Bicyclic Toxin Conjugate	MMAE (Auristatin derivative)	Advanced Solid Tumours (MT1-MMP)	Phase I/II. Example of highly constrained, next-generation peptide platform.	43
CBX-12	Novel Receptor-less Peptide	Docetaxel	Advanced Solid Tumours	Pre-clinical/Phase I. Focuses on novel tumour microenvironment targeting.	44
⁶⁸ Ga-PSMA-11	PSMA-targeting Ligand	Gallium-68 (Radionuclide)	Prostate Cancer (Imaging/Diagnosis)	FDA Approved (2020). Illustrates success in peptide-based diagnostics.	45

Administration routes of PDC:

Given its assured bioavailability, IV Administration is the conventional route for PDCs. On the other hand, it has recently been increasingly explored to make stable PDCs amenable to SC Administration in order to improve patient convenience. Oral Administration, owing to the dual barriers of enzymatic degradation by gastrointestinal proteases and poor permeability across the intestinal epithelium itself, remains largely a developmental barrier⁴⁰. Currently, new strategies are being explored to overcome these limitations, including complexation with anionic nanoparticles. The various route of administration of PDCs are depicted in the fig 3.

RECENT ADVANCES OF PDC IN CLINICAL APPLICATIONS:

The field of PDC is dynamic, and radioligand therapies set the clinical benchmark. The recent advances of PDC in clinical applications is given in table 4.

CURRENT CHALLENGES AND FUTURE DIRECTIONS OF PDC:

PDCs are confronted with several key challenges in current research and development, all of which must be surmounted in order to fully realize their therapeutic potential. The dose-limiting toxicity is primarily nephrotoxicity, arising from the small size of PDCs leading to rapid renal clearance and, consequently, high, transient drug concentrations within the renal tubules⁴⁶. This also leads to a short plasma half-life, severely limiting the time PDCs have in circulation to accumulate effectively at the tumour site, unless chemical stabilizing modifications are utilized. Moreover, the peptide backbone itself faces metabolic instability, as it is highly vulnerable to degradation through systemic proteases and peptidases, thereby reducing its efficacy in vivo. Finally, one of the biological hurdles is tumour heterogeneity, which includes variations in the expression of receptors across different tumour cells and metastatic sites that can compromise targeting efficiency⁴⁷.

To overcome these limitations, three large future directions have come to the fore. First is the design of Next-Generation Peptide Scaffolds, underlining highly constrained structures such as bicyclic and macrocyclic peptides, which confer intrinsic stability against enzymatic cleavage and higher affinity for their targets, as witnessed in new bicyclic toxin conjugates. Development of Smart Linker Systems that take the cue from several concurrent signals from TME⁴⁸-for example, low pH and high concentration of enzymes-will result in higher release specificity and enhanced safety. The most innovative approach is Computational and AI Design, in which AI is incorporated into the de novo design and in silico screening of candidates. This accelerates optimization of lead candidates and advances the capability for prediction of key PK and PD profiles prior to expensive synthesis⁴⁹.

COMPUTATIONAL SOFTWARE AND AI TOOLS:

Optimizing PDCs requires a balance of affinity, stability, and pharmacokinetics-a multiparametric challenge increasingly

addressed by Computational Software and Artificial Intelligence.

- **AI-Driven Peptide Discovery:** ML models perform de novo design by predicting novel peptide sequences with superior characteristics, such as enhanced stability and receptor affinity. This happens faster compared to the traditional methods of screening⁵⁰.
- **Structural Prediction and Optimization:** Programs accurately predict three-dimensional structures of peptide-receptor complexes, which is necessary in rationally modifying the peptide and optimizing linker attachment.
- **In Silico PK/PD Modelling:** ML models simulate and predict the pharmacokinetic profile and pharmacodynamic response of new candidates before synthesis, thereby drastically reducing experimental costs and time⁵¹.

CONCLUSION

The emergence of Peptide-Drug Conjugates (PDCs) marks a significant and powerful progression in the field of precision oncology, firmly establishing them as a crucial targeted therapeutic modality. The profound potential of this platform is not merely theoretical but has been decisively validated by the clinical success of agents such as Lutathera (¹⁷⁷Lu-dotatate), an FDA-approved radioligand therapy. Lutathera, which utilizes a somatostatin analogue peptide to deliver a therapeutic radionuclide to neuroendocrine tumours, serves as a compelling, real-world proof-of-concept, demonstrating the efficacy of using a peptide as a high-affinity homing device.

PDCs possess a unique constellation of inherent advantages that position them favourably against other modalities, including the larger Antibody-Drug Conjugates (ADCs). Crucially, their superior tumour penetration is a key differentiator. The small molecular size of peptides allows them to navigate the dense, high-pressure, and often poorly vascularized tumour microenvironment (TME) more effectively than their macromolecular counterparts, ensuring a more homogeneous distribution of the drug throughout the solid tumour mass.

Furthermore, peptides exhibit low immunogenicity. Unlike large, foreign antibodies, peptides are far less likely to provoke a significant immune response in the patient, reducing the risk of infusion reactions and the formation of anti-drug antibodies (ADAs) that can neutralize the therapeutic agent and accelerate its clearance. This low immunogenic profile contributes to safer administration and potentially allows for repeat dosing regimens. From a practical and commercial standpoint, the scalable synthesis of peptides is another distinct advantage. Peptides can be produced efficiently and affordably using established chemical synthesis techniques, a process that is typically more straightforward and less costly than the complex, biologically-driven manufacturing required for full-length antibodies. These collective advantages solidify the position



of PDCs as key tools in the personalized management of cancer.

Despite the highly promising trajectory, the field is actively working to overcome several engineering challenges. The most prominent of these relates to renal clearance and stability. Due to their small size, PDCs can be rapidly filtered by the kidneys, leading to a short half-life and potential accumulation in the kidneys, which raises concerns about nephrotoxicity. Addressing this requires sophisticated chemical engineering and stabilization techniques. Researchers are employing strategies such as PEGylation (attaching polyethylene glycol chains), lipidation, or designing novel cleavable linkers to increase the molecular size slightly (to slow renal clearance) and enhance *in vivo* stability without sacrificing tumour penetration or targeted release.

The future of PDC development is incredibly bright and is situated at a powerful crossroads of advanced chemistry and the predictive power of Artificial Intelligence (AI). AI and machine learning are increasingly being employed to rapidly screen and optimize peptide sequences for enhanced affinity and stability, to model the kinetics of drug release from the linker, and to predict the optimal physiochemical properties needed for desired half-life and biodistribution. This integration of computational power is accelerating the design-synthesis-test cycle. By leveraging these advanced technologies, researchers are poised to engineer PDCs that are highly stable in the circulation but rapidly activated at the tumour site. Thus, the current momentum suggests that PDCs are not just a temporary trend but are well-positioned to become a staple in future cancer management, offering a refined, powerful, and scalable approach to treating a wide spectrum of malignancies.

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REFERENCES

- Armstrong A, Coburn F, Nsereko Y, Al Musaimi O. Peptide-Drug Conjugates: A New Hope for Cancer. *Journal of Peptide Science*. 2025 Aug;31(8):e70040.
- Wang D, Yin F, Li Z, Zhang Y, Shi C. Current progress and remaining challenges of peptide–drug conjugates (PDCs): next generation of antibody–drug conjugates (ADCs)?. *Journal of Nanobiotechnology*. 2025 Apr 22;23(1):305.
- Cooper BM, Iegre J, O'Donovan DH, Halvarsson MÖ, Spring DR. Peptides as a platform for targeted therapeutics for cancer: peptide–drug conjugates (PDCs). *Chemical society reviews*. 2021;50(3):1480-94.
- Guo S, Wang J, Wang Q, Wang J, Qin S, Li W. Advances in peptide-based drug delivery systems. *Heliyon*. 2024 Feb 29;10(4):e26566.
- Heh E, Allen J, Ramirez F, Lovasz D, Fernandez L, Hogg T, Riva H, Holland N, Chacon J. Peptide drug conjugates and their role in cancer therapy. *International Journal of Molecular Sciences*. 2023 Jan 3;24(1):829.
- Fu C, Yu L, Miao Y, Liu X, Yu Z, Wei M. Peptide–drug conjugates (PDCs): a novel trend of research and development on targeted therapy, hype or hope?. *Acta Pharmaceutica Sinica B*. 2023 Feb 1;13(2):498-516.
- Zhai J, Li Y, Zheng T, et al. The evolution of peptide–drug conjugates (PDCs). *J Peptide Sci*. 2023 Dec;29(12):e24296.
- Alas M, Saghaidehkordi A, Kaur K. Peptide–drug conjugates with different linkers for cancer therapy. *Journal of medicinal chemistry*. 2020 Dec 31;64(1):216-32.
- Goldsmith SJ. Targeted radionuclide therapy: a historical and personal review. *Seminars in Nuclear Medicine*. 2020 Jan 1;50(1):87-97.
- Zhou J, Meng N, Lu L, Lu J, Wu S, Ding Y, Wu S, Bao Y, Xu Q, Chen R, Wang J. A novel peptide–drug conjugate for glioma-targeted drug delivery. *Journal of Controlled Release*. 2024 May 1;369:722-33.
- Olivier T, Prasad V. The approval and withdrawal of melphalan flufenamide (melflufen): Implications for the state of the FDA. *Translational Oncology*. 2022 Apr 1;18:101374.
- McCombs JR, Owen SC. Antibody drug conjugates: design and selection of linker, payload and conjugation chemistry. *The AAPS journal*. 2015 Mar;17(2):339-51.
- Dean TT, Jelu-Reyes J, Allen AL, Moore TW. Peptide–drug conjugates: An emerging direction for the next generation of peptide therapeutics. *Journal of medicinal chemistry*. 2024 Jan 26;67(3):1641-61.
- Al Musaimi O, Lombardi L, Williams DR, Albericio F. Strategies for improving peptide stability and delivery. *Pharmaceuticals*. 2022 Oct 19;15(10):1283.
- Rhodes CA, Pei D. Bicyclic peptides as next-generation therapeutics. *Chemistry—A European Journal*. 2017 Sep 18;23(52):12690-703.
- Noriega HA, Wang XS. AI-driven innovation in antibody–drug conjugate design. *Frontiers in Drug Discovery*. 2025 Jun 26;5:1628789.
- Schlapschy M, Binder U, Börger C, Theobald I, Wachinger K, Kisling S, Haller D, Skerra A. PASylation: a biological alternative to PEGylation for extending the plasma half-life of pharmaceutically active proteins. *Protein Engineering, Design & Selection*. 2013 Aug 1;26(8):489-501.
- Rosen Y, Elman N. *Biomaterials Science*. New York: CRC Press; 2012.
- Amin M, Mansourian M, Koning GA, Badiie A, Jaafari MR, Ten Hagen TL. Development of a novel cyclic RGD peptide for multiple targeting approaches of liposomes to tumor region. *Journal of Controlled Release*. 2015 Dec 28;220:308-15.
- Jadhav K, Abhang A, Kole EB, Gadade D, Dusane A, Iyer A, Sharma A, Rout SK, Gholap AD, Naik J, Verma RK. Peptide–Drug Conjugates as Next-Generation Therapeutics: Exploring the Potential and Clinical Progress. *Bioengineering*. 2025 Apr 30;12(5):481.
- Hoppertz P, Els-Heindl S, Beck-Sickinger AG. Peptide–drug conjugates and their targets in advanced cancer therapies. *Frontiers in chemistry*. 2020 Jul 7;8:571.
- Fotie J, Matherne CM, Mather JB, Wroblewski JE, Johnson K, Boudreaux LG, Perez AA. The fundamental role of oxime and oxime ether moieties in improving the physicochemical and anticancer



properties of structurally diverse scaffolds. *International Journal of Molecular Sciences*. 2023 Nov 28;24(23):16854.

23. Lindberg J, Nilvebrant J, Nygren PÅ, Lehmann F. Progress and future directions with peptide-drug conjugates for targeted cancer therapy. *Molecules*. 2021 Oct 5;26(19):6042.

24. Wang M, Liu J, Xia M, Yin L, Zhang L, Liu X, Cheng Y. Peptide-drug conjugates: A new paradigm for targeted cancer therapy. *European Journal of Medicinal Chemistry*. 2024 Feb 5;265:116119.

25. Song Z, Chen X, You X, Huang K, Dhinakar A, Gu Z, Wu J. Self-assembly of peptide amphiphiles for drug delivery: the role of peptide primary and secondary structures. *Biomaterials science*. 2017;5(12):2369-80.

26. Lelle M, Freidel C, Kaloyanova S, Müllen K, Peneva K. Multivalency: key feature in overcoming drug resistance with a cleavable cell-penetrating peptide-doxorubicin conjugate. *International Journal of Peptide Research and Therapeutics*. 2018 Sep;24(3):355-67.

27. Rajabi M, Adeyeye M, Mousa SA. Peptide-conjugated nanoparticles as targeted anti-angiogenesis therapeutic and diagnostic in cancer. *Current Medicinal Chemistry*. 2019 Sep 1;26(30):5664-83.

28. Mikulová MB, Mikuš P. Advances in development of radiometal labeled amino acid-based compounds for cancer imaging and diagnostics. *Pharmaceuticals*. 2021 Feb 21;14(2):167.

29. Gong L, Zhao H, Liu Y, Wu H, Liu C, Chang S, Chen L, Jin M, Wang Q, Gao Z, Huang W. Research advances in peptide-drug conjugates. *Acta Pharmaceutica Sinica B*. 2023 Sep 1;13(9):3659-77.

30. Guo S, Wang J, Wang Q, Wang J, Qin S, Li W. Advances in peptide-based drug delivery systems. *Heliyon*. 2024 Feb 29;10(4).

31. Egorova VS, Kolesova EP, Lopus M, Yan N, Parodi A, Zamyatnin Jr AA. Smart delivery systems responsive to cathepsin B activity for cancer treatment. *Pharmaceutics*. 2023 Jun 29;15(7):1848.

32. Bariwal J, Ma H, Altenberg GA, Liang H. Nanodiscs: a versatile nanocarrier platform for cancer diagnosis and treatment. *Chemical Society Reviews*. 2022;51(5):1702-28.

33. Chen H, Lin Z, Arnst KE, Miller DD, Li W. Tubulin inhibitor-based antibody-drug conjugates for cancer therapy. *Molecules*. 2017 Aug 1;22(8):1281.

34. Bertozzi CR. A decade of bioorthogonal chemistry. *Accounts of chemical research*. 2011 Sep 20;44(9):651-3.

35. Owoseni OB, Adekiya TA, Akinboye ES, Adesina SK. Development of a Prostate-Specific Antigen Targeted Dual Drug Conjugate for Prostate Cancer Therapy. *ACS omega*. 2025 Apr 25;10(17):17611-25.

36. Huang J, Wu B, Zhou Z, Hu S, Xu H, Piao Y, Zheng H, Tang J, Liu X, Shen Y. Drug-binding albumins forming stabilized nanoparticles for efficient anticancer therapy. *Nanomedicine: Nanotechnology, Biology and Medicine*. 2019 Oct 1;21:102058.

37. Price EW, Orvig C. Matching chelators to radiometals for radiopharmaceuticals. *Chemical Society Reviews*. 2014;43(1):260-90.

38. Lei Y, Zheng M, Chen P, Seng Ng C, Peng Loh T, Liu H. Linker design for the antibody drug conjugates: a comprehensive review. *ChemMedChem*. 2025 Aug 2;20(15):e202500262.

39. Kukis DL, Novak-Hofer I, DeNardo SJ. Cleavable linkers to enhance selectivity of antibody-targeted therapy of cancer. *Cancer Biotherapy and Radiopharmaceuticals*. 2001 Dec 1;16(6):457-67.

40. Nestor J. The medicinal chemistry of peptides. *Current medicinal chemistry*. 2009 Nov 1;16(33):4399-418.

41. Roznovan CN, Măruțescu LG, Gradisteanu Pircalabioru G. Immuno-Oncology at the Crossroads: Confronting Challenges in the Quest for Effective Cancer Therapies. *International Journal of Molecular Sciences*. 2025 Jun 26;26(13):6177.

42. Si Y, Kim S, Ou J, Lu Y, Ernst P, Chen K, Whitt J, Carter AM, Markert JM, Bibb JA, Chen H. Anti-SSTR2 antibody-drug conjugate for neuroendocrine tumor therapy. *Cancer gene therapy*. 2021 Aug;28(7):799-812.

43. Zhu L, Qu J, Tian Q, Qin S, Xu Z, Zhang J, Lu C, Li W. Current research of novel nano-delivery carriers based on exosomes: preparation, targeted enhancement, delivery mechanism and clinical application. *Journal of Materials Chemistry B*. 2026.

44. Geng Q, Sun X, Gong T, Zhang ZR. Peptide-drug conjugate linked via a disulfide bond for kidney targeted drug delivery. *Bioconjugate chemistry*. 2012 Jun 20;23(6):1200-10.

45. Jaradat DS. Thirteen decades of peptide synthesis: key developments in solid phase peptide synthesis and amide bond formation utilized in peptide ligation. *Amino acids*. 2018 Jan;50(1):39-68.

46. Sharma A, Garg P. Convolutional Neural Network: Potential applications in the pharmaceutical sector.

47. Akaiwa M, Dugal-Tessier J, Mendelsohn BA. Antibody-drug conjugate payloads; study of auristatin derivatives. *Chemical and Pharmaceutical Bulletin*. 2020 Mar 1;68(3):201-11.

48. Ding L, Agrawal P, Singh SK, Chhonker YS, Sun J, Murry DJ. Polymer-based drug delivery systems for cancer therapeutics. *Polymers*. 2024 Mar 19;16(6):843.

49. Huang Y, Zhang J, Hou L, Wang G, Liu H, Zhang R, Chen X, Zhu J. Correction to: LncRNA AK023391 promotes tumorigenesis and invasion of gastric cancer through activation of the PI3K/Akt signaling pathway. *Journal of Experimental & Clinical Cancer Research: CR*. 2020 Aug 12;39:155.

50. Lei Y, Zheng M, Chen P, Seng Ng C, Peng Loh T, Liu H. Linker design for the antibody drug conjugates: a comprehensive review. *ChemMedChem*. 2025 Aug 2;20(15):e202500262.

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